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Dobutamine Positron Emission Tomography: Absolute Quantitation of Rest and Dobutamine Myocardial Blood Flow and Correlation With Cardiac Work and Percent Diameter Stenosis in Patients With and Without Coronary Artery Disease

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Objectives. **This study sought to measure myocardial blood flow at rest and during dobutamine infusion and to correlate flow with cardiac work and severity of coronary artery disease.**

Background. **Dobutamine is used with cardiac imaging to induce possible ischemia in patients with known or suspected coronary artery disease. Positron emission tomography permits noninvasive quantitation of myocardial blood flow.**

Methods. **Fifteen patients with quantitative coronary arteriography were studied at rest and during dobutamine infusion using nitrogen-13 ammonia flow imaging with positron emission tomography. Myocardial blood flow was determined in regions corresponding to the three major coronary arteries for myocardium with and without dobutamine flow defects and with and without a >50% diameter stenosis.**

Results. **Eight patients had at least one dobutamine flow defect; four of whom had a previous myocardial infarction. One patient with >50% diameter stenosis had no flow defects, and one with <50% diameter stenosis (48%) had one defect. Dobutamine significantly increased myocardial blood flow in regions with and without a dobutamine flow defect or >50% diameter stenosis, with a greater increase when a defect or >50% diameter stenosis was not present. Rest and dobutamine flows in regions without >50% diameter stenosis were 0.93 ± 0.20 (mean ± SD) and 2.16 ± 0.52 ml/min per g ($p < 0.01$), respectively. The corresponding flows in regions without a defect were 0.94 ± 0.21 and 2.17 ± 0.53 ml/min per g ($p < 0.01$), respectively. This 2.4-fold increase in flow was significantly correlated ($p < 0.001$) with a 2.2-fold increase in rate-pressure product induced by dobutamine. The rest and dobutamine flows for regions subtended by a vessel with >50% diameter stenosis were 0.70 ± 0.33 and 1.20 ± 0.54 ml/min per g ($p < 0.05$), respectively, whereas the corresponding values for regions with a dobutamine flow defect were 0.69 ± 0.33 ml/min per g at rest and 1.23 ± 0.54 ml/min per g during dobutamine ($p < 0.05$). Dobutamine increased flow inversely proportional to percent diameter stenosis. The rest flow for regions with a dobutamine flow defect were not significantly different from that in regions without defects.**

Conclusions. **Dobutamine resulted in a significant increase in myocardial blood flow that correlated significantly with both increased cardiac work and degree of stenosis.**

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Traditionally, patients with known or suspected coronary artery disease perform a stress test to measure the extent and severity of their disease. Treadmill exercise testing has been the standard means of stress, but other forms of stress have been introduced because not all patients are able to perform adequately on the treadmill. Pharmacologic stress testing was introduced using dobutamine, adenosine or dipyridamole for patients unable to adequately perform exercise stress testing. Dobutamine is a synthetic sympathomimetic amine that simulates exercise. Cardiac work and coronary blood flow are increased due to an increase in heart rate and contractility. Dobutamine has been shown to increase myocardial blood flow in proportion to the rate-pressure product in normal volunteers (1). The vasodilators adenosine and dipyridamole do not primarily increase cardiac work; rather, they increase coronary flow because of a direct vasodilator effect on vascular smooth muscle. Stress testing has been combined with echocardiographic and perfusion imaging techniques to enhance the sensitivity and specificity of diagnosing coronary artery disease, as well as to guide future therapy and provide prognostic information.

Positron emission tomography uniquely permits the imaging of flow and metabolism. It has been successfully used with exercise testing (2,3), dipyridamole (4–7) and adenosine (8) to detect significant coronary artery stenoses. Quantification of

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myocardial blood flow has been accomplished using nitrogen-13 (N-13) ammonia as a flow tracer in normal volunteers at rest and during exercise (9), dobutamine (1), dipyridamole (10,11) and adenosine (11). Rest myocardial blood flows have also been reported using N-13 ammonia in patients with a recent myocardial infarction (12). Oxygen-15 (O-15)–labeled water has been used to measure myocardial blood flow at rest and with dipyridamole (13–17). Adenosine and dipyridamole produce greater increases in myocardial blood flow than either exercise or dobutamine (1,9–11,13–17). This is because adenosine and dipyridamole are direct vasodilators and result in maximal myocardial perfusion regardless of demand. Exercise and dobutamine, in contrast, increase myocardial blood flow by directly increasing the cardiac work load, which usually does not result in maximal vasodilation.

Dobutamine is favored by many over the direct vasodilators for pharmacologic stress testing because it more closely simulates exercise. In the current investigation, we studied patients, who had coronary arteriographic data, with positron emission tomography and high dose dobutamine stress testing. Nitrogen-13 ammonia was used as a flow tracer at rest and with dobutamine. The goal was to measure the effect of dobutamine on myocardial blood flow and to determine the correlations among myocardial blood flow, cardiac work and degree of coronary artery stenosis.

Methods

Patients. The study group included 15 patients (mean [±SD] age 62 ± 12 years, range 39 to 80; 13 men, 2 women) who had undergone coronary arteriography for known or suspected coronary artery disease. Written informed consent, approved by the University of California Los Angeles Human Subject's Committee, was obtained from each patient. Four patients had a previous documented myocardial infarction. The clinical characteristics of the patients are shown in Table 1. Subjects were studied in the nonfasting state.

Image acquisition. Patients were positioned in a whole-body tomograph (model 931, CTI/Siemens Gammasonics) that simultaneously acquires 15 transverse slices. The axial field of view is 10.8 cm, and the slices are spaced 6.8 mm apart. The spatial resolution was ~10 mm full width half maximum in plane and ~7 mm in the axial projections. A rectilinear transmission scan was initially obtained to aid in patient positioning within the tomograph. Transmission imaging was performed to correct for photon attenuation.

Study protocol. Each patient received an injection of 15 mCi of N-13 ammonia, delivered by continuous infusion over 30 s, at rest and ~1 h later during peak dobutamine infusion. Dynamic imaging commenced with the onset of each injection. Twelve 10-s images, two 60-s images and one 900-s image were obtained.

Intravenous infusion of dobutamine began at 5 μg/kg body weight per min and was increased in increments of 5 to 10 μg/kg per min every 2 to 3 min to a maximal peak dose of 40 μg/kg per min. Blood pressure and an electrocardiogram were recorded at rest and every 1 to 3 min during the dobutamine infusion. Heart rate and rhythm were continuously monitored. Dobutamine was discontinued if the patient developed one of the following symptoms or findings: moderately severe angina or dyspnea, >2-mm ischemic ST segment depression, frequent ventricular ectopic activity (e.g., short runs of ventricular tachycardia or >5 premature ventricular contractions/min), decrease in blood pressure below baseline, nausea or other uncomfortable side effects of dobutamine, such as flushing or agitation. Nitrogen-13 ammonia was injected at the peak tolerated dose of dobutamine or at 40 μg/kg per min (after it was determined that there were no further increases in heart rate or blood pressure at the 40 μg/kg per min dose). Dobutamine was discontinued 3 min after injection of N-13 ammonia, except in two patients who required discontinuation of dobutamine immediately after the N-13 ammonia injection because of nausea in one patient and slow ventricular tachycardia in another.

Image analysis: polar maps and comparison with normal data base. Transaxial images were reoriented into left ventricular short-axis views using a computer software program developed and previously validated in our laboratory (18,19). The reoriented images were divided into six short-axis planes. The true apex of the heart was not included in the six planes.

Polar maps were generated from the last dynamic image using circumferential profiles of the maximal regional myocardial count activity obtained along 60 equally spaced radians. Assuming that normal myocardium will exhibit the highest flow rates, the rest and dobutamine N-13 ammonia polar maps were then normalized using an average of the top 5% of the N-13 ammonia raw counts for each study to obtain a normalization factor for each study. Data were considered within normal limits if they were within 2 SD of mean normal values previously established in subjects studied at rest.

The polar maps were divided into left anterior descending, circumflex and right coronary artery territories previously established for thallium-201 single-photon emission computed tomographic studies (20). The percent of contiguous pixels with values >2 SD below the mean for normal N-13 ammonia values was calculated for each of the three territories. If >15% of a vascular territory contained contiguous pixels with N-13 ammonia values >2 SD below normal, a flow defect was defined for that vascular territory. The >15% threshold value was chosen to approximate the established threshold value of 60 contiguous degrees (60°/360° = 16.6% of circumference) used in previous work using circumferential profile analyses rather than polar maps (21).

Myocardial blood flow calculation. Myocardial blood flows were calculated using the polar map generated for each dobutamine study as a guide for assigning regions of interest. Regions of interest were identified within each of the three major vascular territories on three short-axis cuts using the following guidelines: A 90° sector region of interest was selected in the mid-left anterior descending coronary artery territory and 60° sectors were selected in both the mid-circumflex and right coronary artery territories unless a dobut-

amine flow defect was evident within a vascular territory. If a dobutamine flow defect was evident within a vascular territory, a sector was defined that included only the defect. If the defect was small, whenever possible an additional region of interest was also drawn to include only the normally perfused myocardium in that vascular territory for the sake of comparison. The sectors defined on the dobutamine N-13 ammonia studies were then applied to all the rest and dobutamine serial N-13 ammonia images to obtain time–activity curves. An N-13 ammonia arterial input function was generated by manually defining a small region of interest (25 mm^2) centered in the left ventricular cavity on the final dynamic rest and dobutamine N-13 ammonia images and applying the same region of interest to all of the serial images. The final frame was used because of clearer definition of the cavity than on earlier images containing fewer counts. The correct position of the blood pool region in the left ventricular cavity was verified on each of the dynamic short-axis image frames. No shift of this region of interest from its central position was observed.

After correcting N-13 ammonia myocardial and blood pool time–activity curves for physical decay of N-13 ammonia, the first 120 s of data from each defined sector were used to calculate myocardial blood flow using a previously validated two-compartment tracer kinetic model (9,18). Nitrogen-13 ammonia is freely diffusible into tissue and becomes trapped in the tissue as N-13 glutamine. The model contains a compartment for freely diffusible N-13 ammonia in tissue, including vascular and extravascular pools, and a second compartment containing the metabolically trapped nitrogen-13. No correction is made for nitrogen-13 metabolites diffusing back into the first compartment. The myocardial time–activity curves were corrected for regional partial volume and spillover of activity from myocardium into the blood pool (18). Myocardial blood flow was determined for each defined sector on three short-axis planes: basal, midventricular and apical. The values presented for each vascular territory are the average myocardial blood flows for the three planes.

Coronary arteriography. Cardiac catheterization with coronary arteriography was ordered by the patient's primary physician because of clinical signs suggesting possible significant coronary artery disease. Quantitative arteriography was applied to the angiograms using a previously described centerline method (22). The area of stenosis was compared with adjacent regions of the vessel without significant stenosis. Automatic edge detection with manual override was used and a geometric method applied. Pincushion distortion corrections were made. Stenosis severity is reported as percent diameter narrowing.

Statistical analysis. Mean values ± SD are reported. Comparisons were made using repeated measures analysis of variance. Least-square regression analysis was used to determine correlation coefficients. A p value <0.05 was considered statistically significant.

Results

Patient response to dobutamine. The rest and peak dobutamine rate-pressure products achieved were 8,423 ± 1,534 and 18,534 ± 4,052 mm Hg × beats/min. Dobutamine infusion was generally well tolerated. The average maximal dobutamine dose received was 35 ± 8 μg/kg per min. Ten of the 15 patients received the maximal dose of 40 μg/kg per min (Table 1). Symptoms or reasons for prematurely discontinuing the dobutamine infusion in the other five patients are shown in Table 1. Nitrogen-13 ammonia was always injected before discontinuation of the dobutamine infusion. In all but two patients (one with nausea, one with slow ventricular tachycardia), dobutamine infusion was continued for an additional 3 min after the N-13 ammonia injection.

Electrocardiographic changes consistent with ischemia were only documented in two patients. Chest pain consistent with angina occurred in three other patients, only one of whom had significant coronary artery disease. Thus, these findings were poor predictors of significant coronary artery disease.

Quantitative arteriography. Quantitative arteriography revealed that 10 of the 15 patients had a quantifiable stenosis in at least one coronary vessel. The degree of percent diameter stenosis ranged from 30% to 100% (Table 2).

Polar map defects. *Rest N-13 ammonia polar maps.* Three patients (Patients 11, 12 and 13) had a total of four flow defects on rest imaging. All rest defects had corresponding dobutamine flow defects. The average defect extent per vascular territory at rest was 45 ± 23% and was not significantly different from the dobutamine defect size of 59 ± 30% in these three patients (Table 3). Two of these patients had a history of a previous anterior myocardial infarction.

Dobutamine N-13 ammonia polar maps. Dobutamine flow defects were identified in 11 vascular territories in 8 (53%) of 15 patients (Table 2). Each defect was associated with a quantitated stenosis ranging from 48% to 100%. A 61% circumflex artery stenosis was not detected in Patient 7, who had a very low dobutamine rate-pressure product. Two patients had contiguous defects present in two vascular territories that were not separated by normally perfused myocardium. These defects represented a single coronary artery stenosis. A 100% circumflex coronary lesion presented as a defect in the inferolateral portion of the right coronary artery distribution. All four patients with a previous myocardial infarction had a dobutamine flow defect in the appropriate distribution, although only two had corresponding rest flow defects.

The average dobutamine defect extent per vascular distribution was 49 ± 21% (Table 3). The average extent was 59 ± 30% and 44 ± 13% for dobutamine defects with and without associated rest flow defects ($p > 0.05$). The extent of the defect was significantly ($p < 0.01$) greater with dobutamine than at rest when all 11 defects were considered or if only dobutamine defects without corresponding rest defects were considered. The subset of three patients with four defects who had both

Table 1. Clinical Characteristics of 15 Study Patients

Pt No.	Age (yr)/ Gender	ECG	CP	Peak Dob	Symptoms and/or D/C Reason	RPP With Dob	Rest EF (%)		Rest WMA	MI
							Cath	Echo		
1	69/M	ND	−	40		23,940	62	63	BIM	−
2	39/M	−	+	40		18,720	NA	66		−
3	52/M	−	−	40		20,960	NA	62		−
4	62/M	−	−	40		21,824	64	65		−
5	50/F	−	+	30	Anxiety, palpitations	15,080	75	69		−
6	70/M	−	−	40		19,880	60	67		−
7	54/M	−	−	40	Headache	10,248	55	65	BIM	−
8	69/F	+	−	30	Nausea	20,700	NA	64		−
9	46/M	−	−	40	Sweating, rapid breathing	18,720	63	56		−
10	80/M	−	−	40		21,590	25	32	Diffuse	Ant
11	67/M	−	−	15	Target HR	22,892	38	58	Ant/apex	Ant
12	71/M	−	−	30	PVCs	16,632	43	49	Ant/apex	Ant
13	68/M	−	−	20	Slow VT	10,500	58	62	Apex/BIM	−
14	78/M	−	+	40		18,020	NL	62		−
15	51/M	+	−	40		18,312	67	64	Apex/BIM	NQ
Mean	62			35		18,543	55	60		
SD	12			8		4,052	15	9		

Ant = anterior wall; BIM = basal inferomedial wall; Cath = catheterization; CP = presence of chest discomfort during dobutamine infusion; D/C Reason = reason for discontinuing dobutamine before peak dose; Dob = dobutamine; ECG = ischemic ST segment changes during dobutamine infusion; Echo = echocardiography; EF = ejection fraction; F = female; HR = heart rate; M = male; MI = previous myocardial infarction; NA = not available; ND = nondiagnostic; NQ = non-Q wave; Peak Dob = maximal dose of dobutamine received by patient (μg/kg per min); Pt = patient; PVCs = premature ventricular contractions; RPP = rate-pressure product (beats/min × mm Hg); VT = ventricular tachycardia; WMA = wall motion abnormality; + = present; − = absent.

rest and dobutamine defects did not exhibit a significant difference.

Myocardial blood flow. The rest and dobutamine myocardial blood flows are presented in Table 2 for each vascular territory. If it was not possible to define a region of interest without a dobutamine flow defect within a vascular territory, then no flow is shown for rest and dobutamine myocardial blood flow (Table 2). The average rest myocardial blood flows were not significantly different ($p > 0.05$) among the three vascular territories. The average rest and dobutamine flows for all territories, excluding defect flows, in the 15 patients were 0.94 ± 0.21 and 2.17 ± 0.53 ml/min per g, respectively, and were significantly different from each other ($p < 0.01$). Rest and dobutamine flows in regions without >50% diameter stenosis were 0.93 ± 0.20 and 2.16 ± 0.52 ml/min ($p < 0.01$). The average myocardial blood flow increased 2.4-fold with dobutamine and correlated significantly (correlation coefficient 0.93, $p < 0.001$) to the 2.2-fold increase in the rate-pressure products also presented in Table 2. The individual rate-pressure products and corresponding myocardial blood flows are plotted in Figure 1.

Myocardial blood flows for regions of interest defined as exhibiting dobutamine flow defects are listed under Defect MBF in Table 2. For comparison, the rest flows for the same regions of interest are also listed. The myocardial blood flows for defects exhibited considerable variation and averaged 0.67 ± 0.35 ml/min per g at rest and 1.20 ± 0.57 ml/min per g with dobutamine. The dobutamine-induced increase in blood flow in the defect regions was significant ($p < 0.05$). Myocardial blood flows for defect regions are plotted against rate-pressure products in Figure 1 (correlation coefficient 0.61, $p < 0.01$). Defect flow was normalized to the average flow in territories without significant stenoses for each patient and is also presented in Table 2. Defect myocardial blood flows compared with average flows for myocardium without defects were not significantly decreased on average at rest ($p > 0.05$) but were significantly decreased with dobutamine ($p < 0.01$). On average, rest and dobutamine defect myocardial blood flows were 24% and 41% lower, respectively, than the patient's average rest and dobutamine myocardial blood flows for territories without defects. The corresponding rest and dobutamine flows for regions subtended by a vessel with >50% diameter stenosis were 0.70 ± 0.33 and 1.20 ± 0.54 ml/min per g ($p < 0.05$).

Myocardial blood flow at rest and with dobutamine for regions of interest supplied by vessels with stenoses of any degree are plotted against the percent diameter stenosis in Figure 2. No significant correlation was present for the rest flow data, but the dobutamine myocardial blood flow was inversely correlated with the percent diameter stenosis (correlation coefficient 0.63, $p < 0.02$).

To examine the correlations among rate-pressure product, myocardial blood flow and percent stenosis, the ratio of the absolute change in myocardial blood flow and the absolute change in rate-pressure product for each patient using the average flows in myocardium without perfusion defects was calculated. This ratio was also calculated for each quantitated stenosis. The inverse relation between this ratio and percent diameter stenosis was significant and is presented in Figure 3 (correlation coefficient 0.65, $p < 0.001$).

Table 2. Rate-Pressure Product and Myocardial Blood Flow in 15 Study Patients

Pt No.	RPP			Rest MBF				Dob MBF				AVG D/R MBF	Defect MBF		Defect/AVG MBF		Dob Defect Location	Stenosed Vessel (% diameter stenosis)
	Rest	Dob	D/R	LAD	Cx	RCA	AVG	LAD	Cx	RCA	AVG		Rest	Dob	Rest	Dob		
1	10,920	23,940	2.2	1.01	1.16	0.97	1.05	2.26	2.56	2.21	2.34	2.2					None	
2	7,194	18,720	2.6	0.82	0.63	0.81	0.75	2.16	1.95	1.99	2.04	2.7					None	
3	9,963	20,960	2.1	1.42	1.42	1.27	1.37	2.66	2.40	2.51	2.52	1.8					None	
4	8,280	21,834	2.6	0.85	1.03	0.43	0.77	2.12	2.38	1.99	2.16	2.8					None	
5	8,816	15,080	1.7	1.10	1.11	0.90	1.04	2.28	2.25	2.16	2.23	2.2					None	
6	8,970	19,880	2.2	1.19	1.00	1.13	1.11	2.76	2.57	3.27	2.87	2.6					None	41 LAD
7	6,273	10,248	1.6	0.83	0.90	1.10	0.94	1.42	1.21	1.50	1.38	1.5					None	61 prox Cx/62 prox OM2
8	9,455	20,700	2.2	1.21	1.19		1.20	2.27	1.97		2.12	1.8					None	48 mid-LAD
													0.85	1.44	0.71	0.68	RCA	48 mid-RCA
9	6,000	18,720	3.1	0.71	0.71	0.67	0.70	1.72	2.70	1.45	1.96	2.8	0.36	0.96	0.51	0.49	LAD/RCA*	55 prox LAD
10	10,500	21,590	2.1		1.17	1.07	1.12		3.02	2.67	2.85	2.5	1.23	2.27†	1.10	0.80	LAD	58 prox LAD
11	9,324	22,892	2.5		0.86	0.98	0.92		3.02	2.49	2.76	3.0	0.53‡	0.78†	0.58	0.28	LAD	70 prox LAD
12	7,705	16,632	2.2		0.67	0.66	0.67		1.78	1.43	1.61	2.4	0.16‡	0.75†	0.24	0.47	LAD/RCA*	67 prox LAD
13	6,160	10,500	1.7	0.82		0.77	0.80	1.21		1.20	1.21	1.5	0.65‡	0.95	0.81	0.79	RCA	100 Cx
14	8,556	18,020	2.1	0.69	0.76		0.73	2.61	2.90		2.76	3.8	0.73	1.91	1.00	0.69	RCA	67 mid-RCA
15	8,235	18,312	2.2	1.09		0.74	0.92	1.76		1.83	1.80	2.0	0.67	1.10†	0.73	0.61	LAD	100 LAD
													1.06	0.90	1.15	0.50	Cx	99 Cx
																		30 RCA
Mean	8,423	18,534	2.2	0.98	0.97	0.88	0.94	2.10	2.36	2.05	2.17	2.4	0.69	1.23	0.76	0.59		
SD	1,534	4,052	0.4	0.23	0.24	0.23	0.21	0.49	0.53	0.59	0.53	0.6	0.33	0.54	0.30	0.17		

*Contiguous defects. †Previous myocardial infarction. ‡Rest perfusion defect also present. AVG = average; Cx = circumflex artery; Defect/AVG MBF = defect myocardial blood flow (ml/min per g) divided by average myocardial blood flow for normally perfused myocardium for the same patient; D/R = ratio of dobutamine and rest values; LAD = left anterior descending coronary artery; OM2 = second obtuse marginal branch; prox = proximal; other abbreviations as in Table 1.

Table 3. Extent of Defects on Rest and Dobutamine Images

Category	No. of Defects	Extent of Defect (%) Rest (mean ± SD)	Dobutamine (mean ± SD)
All dobutamine defects	11	21 ± 24	49 ± 21*
No rest defect; dob defect only	7	7 ± 6	44 ± 13*
Rest and dob defects	4	45 ± 23	59 ± 30

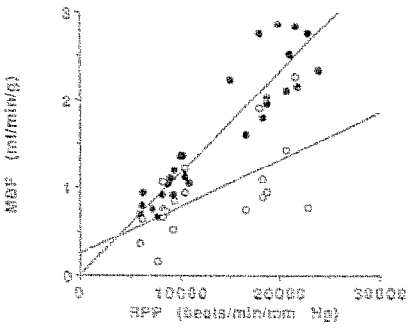
*$p < 0.01$, rest versus dobutamine (dob).

Discussion

Quantitation of myocardial blood flow. To our knowledge, this study is the first attempt to quantitate myocardial blood flow with N-13 ammonia in patients with coronary artery disease at rest and with dobutamine. Myocardial blood flow and cardiac work, as represented by the rate-pressure product, were closely correlated in vascular territories without defects. These results are similar to those previously reported and similarly obtained in normal young volunteers (25 ± 6 years old) (1). A similar correlation was also present in regions of interest corresponding to dobutamine flow defects, although the absolute increase in defect flows with dobutamine was smaller. In addition, our study has demonstrated that dobutamine myocardial blood flow is closely correlated with degree of stenosis. Thus, dobutamine increases flow in proportion to the demand, but this increase is modulated by degree of stenosis present.

Prior myocardial infarction. The site of a previous myocardial infarction can contain both viable and nonviable myocardium. Flow is expected to be decreased to nonviable myocardium. Our study was not designed to investigate this issue and included only four patients with a previous myocardial infarction. However, we can state from our limited data that a previous myocardial infarction is not uniformly detected as a rest flow defect. We also did not uniformly detect a significant reduction in dobutamine flow in the area of a previous infarction, despite the presence of wall motion abnormalities.

Figure 1. Myocardial blood flow (MBF) is plotted against rate-pressure product (RPP) for vascular regions of interest without (**solid circles**) and with a dobutamine flow defect (**open circles**).



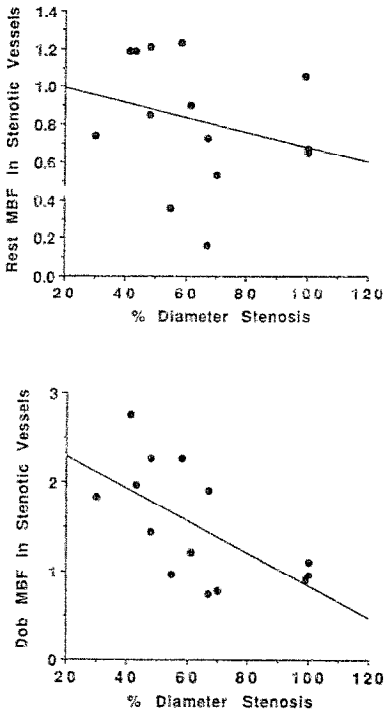


Figure 2. Myocardial blood flow (MBF) is plotted for regions supplied by a stenotic vessel versus percent diameter stenosis at rest (**top**) and with dobutamine (**bottom**). The correlation coefficients are 0.26 (**top**) and 0.63 (**bottom**), with p values of 0.30 (**top**) and <0.02 (**bottom**).

Comparison with dipyridamole studies. Studies using N-13 ammonia or O-15–labeled water to quantitate myocardial perfusion in patients with coronary artery disease at rest and with dipyridamole have similarly demonstrated a significant decrease in the expected augmentation of myocardial blood flow with dipyridamole in the distribution of stenotic vessels (14–16,23).

Dobutamine-induced increases in myocardial blood flow are proportional to cardiac work. This increase in flow rarely approaches the threefold or greater potential increase in myocardial blood flow that can be obtained with vasodilators. Thus, dobutamine does not result in measurement of myocardial blood flow reserve. Our study suggests that it is not necessary to measure the myocardial blood flow reserve to assess the severity of coronary stenoses. Comparison of dobutamine flows in defect areas with dobutamine flows where no defect is present accomplishes the same goal. However, as is true for all noninvasive testing, this technique may result in false-negative results if an inadequate rate-pressure product is achieved with dobutamine. If clinically feasible, avoidance of beta-blockers may eliminate some of the low rate-pressure products. Also, intravenous atropine can be cautiously administered in selected patients without contraindications to increase the heart rate when chronotropic incompetence is present.

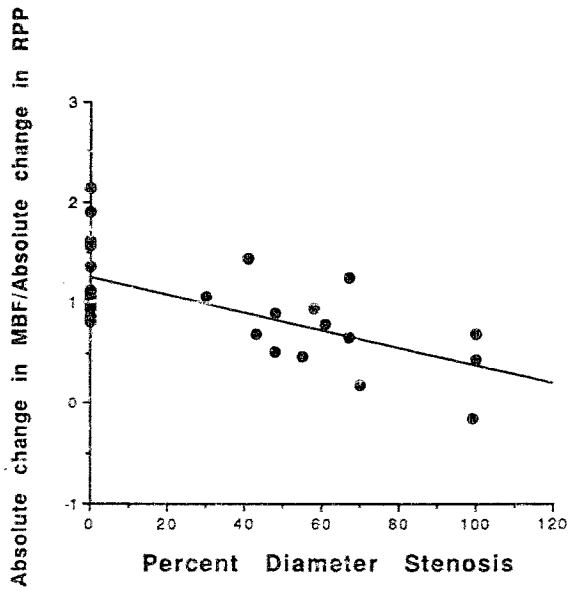


Figure 3. Absolute change in myocardial blood flow (MBF) divided by absolute change in rate-pressure product (RPP) is plotted for each patient (using the average myocardial blood flow in myocardium without a dobutamine defect) and for each detected stenosis versus the measured percent diameter stenosis. When a stenosis was not detected for quantitation, the percent diameter stenosis was assumed to be 0% (correlation coefficient 0.65, $p < 0.001$).

Limitations of the study. Detection of flow defects relied on vascular territories validated for single-photon emission computed tomography but not for positron emission tomography. Given the inherent variability and overlap in vascular territories, it is expected that the territories defined by each technique will not be unique but will be similar to each other. Moreover, although we carefully adhered to these defined territories for purposes of this study, interpretation of clinical studies requires that attention be given to defects that straddle defined vascular territories even if the percent involvement in each territory is ≤15%.

The data base compiled in our laboratory and used to define abnormal patient responses was created using nonfasting, normal volunteers studied with N-13 ammonia at rest (10). Ideally, we would have had a data base of age-matched, normal volunteers who had been studied with dobutamine, but such a data base is not available. All comparisons with the normal data base used normalized data. We compared both rest and dobutamine flow images with the previously obtained normal volunteer rest flow images and assumed that normalized dobutamine-induced flow increases would follow the same distribution exhibited on rest studies. There is no obvious reason to suspect that the normalized dobutamine flows would differ from the rest flow distributions. (Dobutamine polar maps from five normal volunteers from a previous study that were compared with the currently used data base fell within the normal distribution.)

Dobutamine increases contractility in normally perfused myocardium and can result in decreased contractility in myocardium which becomes ischemic. Therefore, changes in wall motion are expected with dobutamine that were not present at rest. Ideally, measurement of wall thickness and thickening should be made for each segment at rest and with dobutamine so that corrections can be made for partial volume effects. Unfortunately, the means for such corrections are not available at this time. Despite the lack of these corrections, the directional changes in flow measured in this study correlated with cardiac work and degree of stenosis. Inaccuracies in flow measurements can also result because the partial volume effects related to an area of thinned, infarcted myocardium are not appropriately estimated.

Summary. Myocardial blood flow in patients with suspected coronary artery disease increased with dobutamine in proportion to the increase in cardiac work and were inversely proportional to the degree of stenosis. The physiologic severity of the stenosis in terms of absolute flow reduction was directly assessed. No other noninvasive technique can accomplish this goal.

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